Dry Powder Aerosols: Emerging Technologies

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INTRODUCTION

The delivery of pharmaceutical aerosols as a dry powder is no longer perceived as the "second best" method to deliver drugs to the lung. This is because of the mounting technologies, which are capable of making stable powders of respirable size and devices competent to deliver accurate doses and versatile payload.

The identification of the lung to deliver drugs to the bloodstream has expanded the kinds of chemical entities that can be delivered via this route. Therapeutic proteins and polypeptides such as insulin administered as a powder via the lung are examples showing substantial systemic absorption into the bloodstream, resulting in well-controlled blood glucose level for diabetes.[1,2]

The delivery of therapeutic macromolecules by inhalation, however, presents additional problems and challenges to produce fine powders of particle size 0.5 μm–5 μm that flow well during manufacture, filling, and emptying from the inhaler device. Macromolecules are more "fragile" compared with small molecules, thus imposing certain restrictions during manufacture and storage in order to maintain not only their dispersibility, but also their biochemical and physical stability. Proteins and polypeptides are often substantially more expensive than the small molecules; therefore, the ability to efficiently deliver the dry powder with minimal loss is crucial. Furthermore, adequate dispersion and delivery of the powder to the patient are especially important for reproducible lung distribution and systemic absorption of drugs.

This review captures some of the most recent technologies with examples relating to pharmaceutical dry powder aerosol delivery.

EMERGING TECHNOLOGIES FOR POWDER AEROSOL DELIVERY

Two main areas that have been given most attention to improve inhalation drug delivery of powders are: (I) powder production and formulation and (II) powder inhaler devices.

Powder Production and Formulation

Traditionally, freeze-drying has been the process used to produce dry powders of proteins and peptides from a solution. This is because the solution can be dried without being exposed to elevated temperatures, which may adversely affect the product stability. Unfortunately, powders prepared by this method are too large in size for inhalation. Even though milling of the freeze-dried powders to reduce particle size is feasible, the pressure, temperature, and shear resulting from milling may cause significant loss of bioactivity of proteins.[3,4]

To date, the two most successful ways for making powders for inhalation are spray drying and solvent precipitation.

Spray drying

Spray drying involves converting the atomized liquid droplets into dry powders by hot air. This one-step process is capable of making particles of size suitable for inhalation.[5] The particle size and size distribution of the powder can be manipulated by the concentration of the feed solution, the spray temperature, cyclone efficiency, and chemical nature of the feed.[6]

Therapeutic proteins prepared as dry powders are often found unstable when dried alone. Due to the tremendous surface area of the atomized droplets and the relatively high drying temperatures and mechanical stress during atomization, the integrity of the protein may be adversely affected during spray drying. Protein degradation can be minimized by cospray drying the protein with excipients as has been reported for recombinant human deoxyribose nuclease (rhDNase) for inhalation.[7,8]

Molecular aggregation of recombinant human growth hormone (rhGH) due to air–liquid interfacial degradation can be prevented by adding polysorbate-20 (with no sugar protectant) or Zn^{2+} into the liquid feed. Polysorbate-20 significantly reduced the formation of insoluble protein aggregates, while Zn^{2+} suppressed the formation of soluble protein aggregates. Combination of polysorbate-20 and Zn^{2+}

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resulted in a spray-dried rhGH powder having insignificant protein degradation. The occupancy of polysorbate at the air–liquid interface of spray droplets and the formation of a dimer complex between Zn^{2+} and rhGH are believed to reduce the chance for protein unfolding and aggregates formation.[9]

Spray drying of recombinant humanized monoclonal antibody, anti-IgE (rhMAbE25) containing trehalose or lactose had $\leq$1% of aggregates formed following spray drying.[10] Despite that, the powders containing trehalose were too cohesive for aerosol delivery. Mannitol was less capable of stabilizing rhMAbE25, with 1%–3% aggregates found following spray drying. The stabilizing effect of mannitol leveled off at a mannitol concentration of $\sim$20 wt. %.[11] In the case of follicle stimulating hormone (FSH), formulation containing mannitol, sucrose, and raffinose as excipients gave rise to $\leq$2% of the higher order aggregates formed from spray drying. Mannitol-containing formulations had the highest amount of aggregates (1.2%) than those of sucrose and raffinose (0.05%). The production yield of powders from the mannitol-containing formulation (50%) was much less than that of sucrose (79%) and raffinose (74%). Despite these, the mannitol-containing formulation has the highest emitted dose of 66 wt. % vs. 15 wt. % and 55 wt. % obtained from the sucrose- and raffinose-containing formulation, respectively.[12] These results indicate that each protein/excipient system requires individual characterization to identify an optimal formulation for powder aerosol performance and protein stability.

Modification of the spray drying process

Spray Freeze-Drying. Spray freeze-drying, a method developed for producing protein aerosol powders, involves spraying the feed solution into liquid nitrogen followed by freeze-drying. This process produces large ($\sim$8 μm–10 μm) but porous particles of rhDNase and anti-IgE with high production yields ($>$ 95%). The fine particle fraction (FPF) of the spray freeze-dried powder was significantly higher than that of the spray-dried powder due to improved aerodynamic properties.[13] The overall process, however, is much more costly, time consuming, and complex as compared with spray drying.

Process for Spray Drying Hydrophobic Drugs. The conventional spray drying process is usually limited to hydrophilic drugs with hydrophilic excipients in aqueous solutions. It is not feasible for systems containing hydrophobic drugs and hydrophilic excipients or vice versa. While spray drying of hydrophobic materials can be accomplished using an organic solvent, a patented invention has been developed for spray drying pharmaceuticals and other compositions, which comprise both hydrophobic and hydrophilic substances. A basic requirement is that the hydrophilic excipient and hydrophobic drug would be at least partially dissolved in the same organic solvent or cosolvent system.[14] For example, both budesonide (hydrophobic drug) and povidone (hydrophilic excipient) have high solubility in methanol. Such a drug/excipient composition yielded powders of slightly dimpled spheres, with moisture content of 0.49 wt.%, and particle size of 2.3 μm. The delivered dose efficiency was measured as $\sim$ 50 wt.%. The use of a nonaqueous or partially aqueous system has the advantage of preparing powders that are physically or chemically sensitive to water while in solution or to residue moisture in the powder.

Solvent precipitation

The solvent precipitation method utilizes the unique properties of nonsolvent at a critical temperature and pressure to precipitate solid particles of drugs from solutions. Carbon dioxide, which exhibits remarkable solvent power at its critical temperature of 31.1°C and pressure of 70 bar for high molecular weight and low vapor pressure solids, is an ideal nonsolvent choice. CO_2 is also nontoxic, inexpensive, and readily available. Technical details of supercritical fluid technology can be found in Vol. 18 of this encyclopedia series.[15] The technology has been successfully applied to the production of fine particles for aerosol delivery.[16–18]

York and Hanna[17] have developed the SEDS (solution enhanced dispersion by supercritical fluids) process for preparing powders of an anti-asthmatic drugs salmeterol xinafoate. The method is capable of controlling the dispersion of the solution in the system, and thus has the ability to manipulate the characteristics of the particles in the micrometer-sized range. This technique has also been used to prepare powders of therapeutic proteins, with the key experimental component being the three-channeled coaxial nozzle designed to use high velocity supercritical CO_2 to disperse the feed of aqueous and organic nature into the particle formation vessel. Relatively high percent of bioactivity was maintained for lysozyme and a therapeutic peptide (95% and 100%, respectively).

Alternatively, protein particles can be produced using a supercritical or near critical CO_2-assisted aerosolization and bubble drying process.[20] This method utilizes the high solubility of CO_2 in water, coupled with expansion of the solution through a nozzle to aerosolize aqueous solutions of drugs. When the microbubbles formed are dried, solid (such as lactose and albuterol sulfate, with size between 0.5 μm and 5 μm) or hollow spherical particles (such as sodium

chloride, mannitol, or tobramycin sulfate) are formed depending on the compound. Protein powders such as lysozyme or lactate dehydrogenase can also be produced by this process and can be stabilized through the use of sugars, buffers, and surfactant additives in the formulations. Depending on the solute and conditions of drying, the particles are crystalline in some cases and amorphous in others.[21]

Recently, Bustami et al.[22] have investigated the feasibility of the ASES (aerosol solvent extraction system) process to generate microparticles of proteins for inhalation. Protein powders generated were of particle size 100 nm–500 nm. In vitro performance showed 65, 40, and 20 wt. % res pirable fraction for lysozyme, albumin, and insulin, respectively. Little or no loss of monomer content was observed for these proteins.

Ways to improve powder flowability and dispersability

Inclusion of Excipient. Powders prepared by any one of the above methods may not be used directly as the powders may be too cohesive for device filling and for administration as an aerosol. This is the case for anti-IgE cospray dried with trehalose[10] and spray-dried rhDNase powders.[8] In contrast to the traditional approach of using binary blend systems (i.e., drug plus coarse carrier), the addition of fine carrier particles ($< 10\ \mu m$) such as lactose and magnesium stearate to form a ternary system has been shown to further enhance the amount of drug particles in the aerosol cloud.[23,24] The role of the fine carrier particles is believed to reduce the drug–coarse carrier interaction by occupying possible drug binding sites on the larger carrier particles. The formation of multiplets between the fine carrier and drug may hinder the direct contact between the drug and the coarse carrier, thus promoting detachment of drug particles from the carrier surface during powder dispersion. Magnesium stearate at concentration as low as 0.1% was found to be sufficient to increase the fine particles of salbutamol sulphate in the aerosol cloud.[24]

Recently, Ganderton et al.[25] have found that the inclusion of low-density amino acid particles produced by spray drying can also enhance the amount of fine particles in the aerosol. Such low-density, flake-like particles have a bulk density of 0.1 g/mL with thickness of $\leq 100\ \mu m$ and $MMAD \leq 10\ \mu m$. Addition of low-density leucine particles as low as 1% enhances the fine particles of salbutamol in the aerosol by $\sim$25 wt. %. However, the addition of 10% leucine made no difference to the amount of fine particles in the aerosol compared with salbutamol alone.

Another conventional approach to improving powder flow and dispersion is to form agglomerates. However, liquids that are commonly used, e.g., alkanols, may dissolve and denature the actives such as macromolecules. The recent discovery of fluorocarbon (FC) liquids including perfluorodecalin and perfluorooctyl bromide as alternatives may be useful because they are hydrophobic and do not dissolve proteins. In addition, FC has a low surface tension; relatively weak bonds are expected to form between the fine particles of the loose agglomerates, which can be then redispersed readily as an aerosol. The high vapor pressure of FC renders low solvent residue in the final product.[26] Fluorocarbon does not contain chlorine atoms, and is therefore ozone friendly.

Tailor-made powders

Besides the use of excipients, powder flow and dispersion can also be improved by manipulation of the physical characteristics of the powder.

AIR™ Particles. AIR™ particles (Alkermes, Inc., Cambridge, Massachusetts, U.S.A., Fig. 1) are prepared by spray drying solutions containing a mixture of drug and biodegradable material (e.g., polyglycolic acid, polylactic acid, or copolymers). AIR™ particles have a low tapped density of less than $\sim 0.4\ g/cm^3$, with an irregular surface. These low-density particles are physically large but aerodynamically small, which enhances the flow and dispersion of powders, and are ideal for deep lung delivery. Large particles could also minimize phagocytic uptake in alveoli, thereby providing the potential for controlled release of drugs in the lungs.[27,28]

Pulmosphere™. Pulmosphere™ (Inhale Therapeutic Systems, San Carlos, California, U.S.A.) particles are also prepared by spray drying, in which the feed

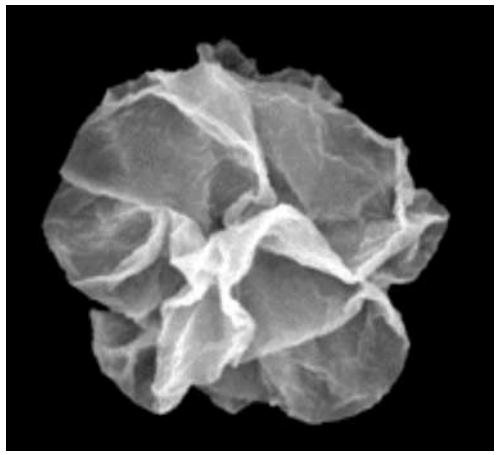


Fig. 1 AIR™ particle. (Courtesy of Alkermes, Inc., Cambridge, Massachusetts, U.S.A.)

comprises an aqueous solution containing dissolved or dispersed active drug, and a fluorocarbon-in-water emulsion, stabilized by a monolayer of phospholipid (such as dipalmitoylphosphatidylcholine).[29] Being hollow and porous, Pulmosphere™ particles have a bulk density of $0.05\ g/cm^3 - 0.2\ g/cm^3$, and a size between 2 μm and 4 μm. These particles are dispersed more readily without the need of carriers than the traditional drug–carrier blends with lactose.

Wrinkled Surface Particles. In contrast to the AIR™ particles and Pulmospheres™ which are hollow and porous, *solid* protein particles with wrinkled surfaces have recently been prepared in our laboratory. These wrinkled particles gave a significant improvement in FPF over spherical particles of bovine serum albumin.[30] The reduction of the surface contacts among the wrinkle particles (Fig. 2) is believed to reduce powder cohesion. Dispersion of the wrinkle particles was shown to be less dependent on the inhaler choice and airflow compared with the smooth spherical particles of the same aerodynamic size.

Powder Inhaler Devices

Dry powder preparation and formulation are only part of the inhalation drug delivery system. Dispersion of these powders is closely linked to the performance of the inhaler device.

Recent inventions of the powder inhaler device are aimed at improving the inhaler's dispersion efficiency and reducing the resistance of the device as well as decoupling powder dispersion from the patient's inspiratory effort in order to deliver accurate and flexible dosages for different patient's needs.

Innova™ and Solo™

The Innova™ (Inhale Therapeutic Systems, San Carlos, California, U.S.A., Fig. 3) inhaler device is a unit dose inhaler that has been designed for long-term use. It is powered by a stored bolus of compressed air and is designed to generate aerosol independent of patient's inspiratory effort. A transparent holding chamber enables patients to view

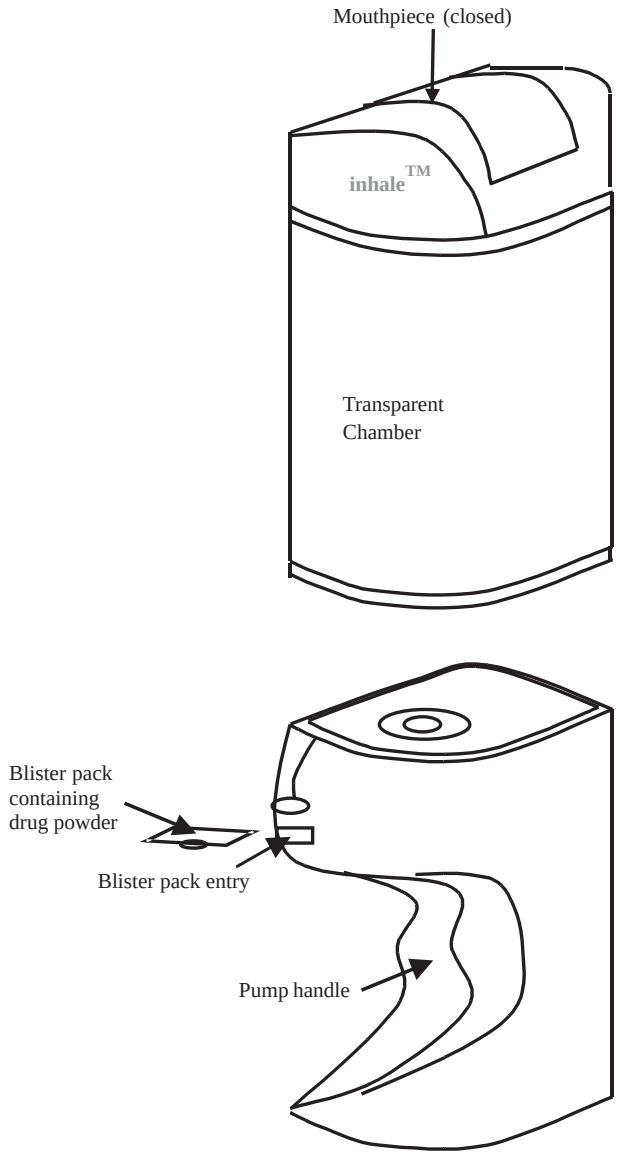


Fig. 3 Schematic diagram of Innova™ from Inhale Therapeutic Systems. (Adapted from Ref. 32.)

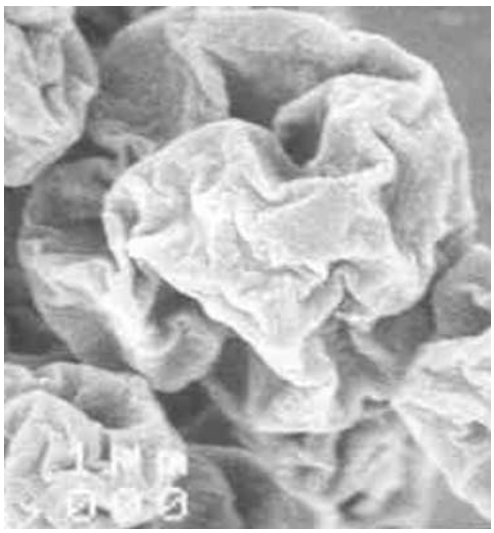


Fig. 2 Wrinkled bovine serum albumin particles, produced by spray drying.

the aerosol to assure proper dosing. Further, the device is designed to have the capability to fluidize and extract up to 90% of the dose from the reservoir, thus minimizing waste and enhancing the accuracy and precision of the dosage.[31]

The Solo™ device from Inhale Therapeutic Systems is a patient-driven unit dose inhaler. It has a built-in flow control to maximize the reproducibility of dose to patient. It is designed for short-term use and when large drug dosages are preferred.[32]

SkyePharma mDPI

SkyePharma multidose pocket-sized inhaler features an "intelligent" single dose counter to count the dose dispensed and remained in the inhaler. The built-in locking mechanism also allows no "tailoff" effect toward the last doses from the inhaler[33] (Fig. 4).

Bead inhaler technology

Elan Pharmaceuticals has developed the Spiros® S2 inhaler which features the use of beads to disperse the powders on inhalation. Still under development, the results from testing show that Spiros® S2 is a high dispersion efficiency inhaler capable of delivering drugs at relatively low inspiratory flow rates (30 L/min and 60 L/min).[34]

Twisthaler®

The Twisthaler® (Schering-Plough, Kenilworth, New Jersey, U.S.A., Fig. 5) features specially designed nozzle geometry that creates an airflow pattern which carries the small particles out of the device via the fluted chimney, while the larger particles or agglomerates will be spun into a centrifugal pattern and deagglomerated into fine particles for inhalation. The design optimizes the deagglomeration of powders, but at the same time minimizes drug caught in the inhaler nozzle and mouthpiece.[35]

Fig. 4 SkyePharma mDPI. (Courtesy of SkyePharma, PLC, Switzerland.)

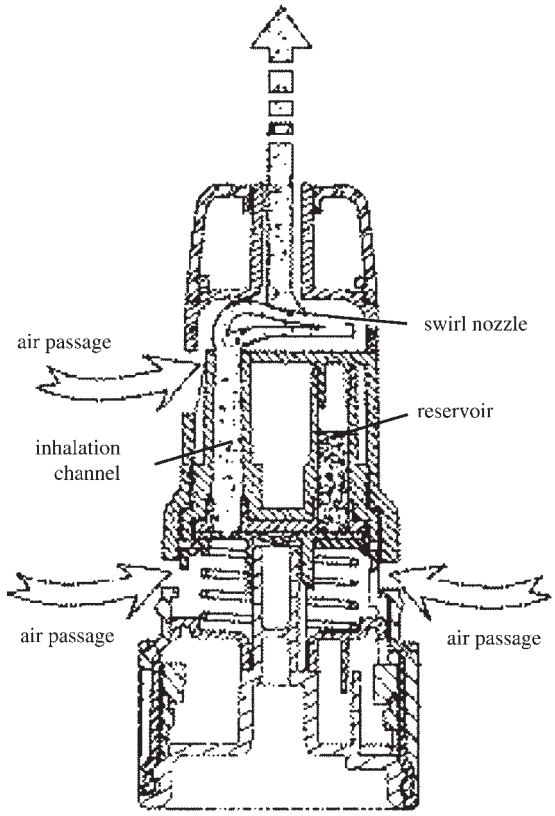


Fig. 5 Inhalation through the ASMANEX™ TWISTHALER™ DPI. (From Serentec Press, Raleigh, North Carolina.)

Hovine FlowCaps®

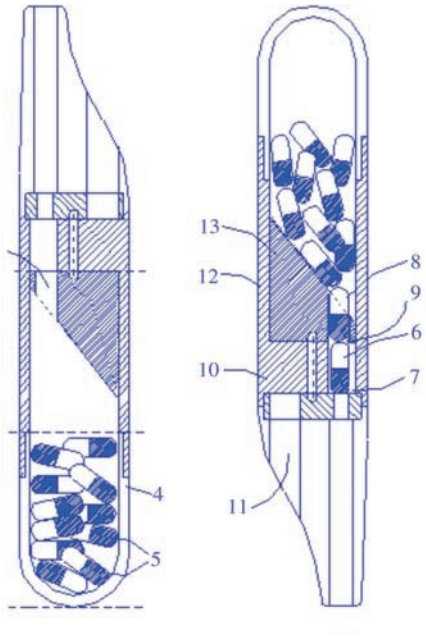
Hovine FlowCaps® (Hovione SA, Loures, Portugal, Fig. 6a and b) is a capsule–powder inhaler. Instead of the traditional needle piercing, the capsule is pierced by two blades, giving rise to a narrow slit across each end of the capsule. The tube-shaped inhaler receives the capsule(s) at one end.[36,37] Upon inhalation, the air is mainly entrained into the inhaler tube inlets, with only a little air entering the capsules. The powder gets fluidized and experiences turbulence within the capsule before emptying from the device.

Random Loading

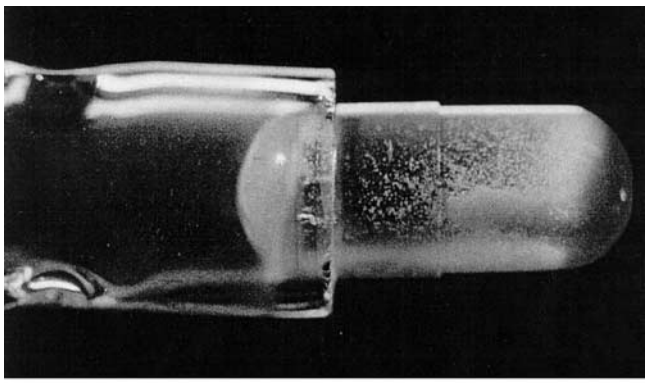
Capsules do not have to be inserted in a proper orientation, as in all other capsule based systems.

A patented ramp will automatically right a capsule for loading into the inhalation chamber.The patient can visually check that this is happening.

Ease of use is fundamental for patient compliance.



(a)



(b)

Fig. 6 (a) Hovione SA FlowCaps® dry powder device. (Courtesy of Hovione Productos Farmaceuticos SA, Portugal.) (b) Photograph showing the dispersion of powders within the capsule in a Hovione SA FlowCaps dry powder inhaler. (Courtesy of Hovione Productos Farmaceuticos SA, Portugal.)

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